General

Guideline Title

Assessment: symptomatic treatment for muscle cramps (an evidence-based review). Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.

Bibliographic Source(s)

Katzberg HD, Khan AH, So YT. Assessment: symptomatic treatment for muscle cramps (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2010 Feb 23;74(8):691-6. [36 references] PubMed

Guideline Status

This is the current release of the guideline.

The American Academy of Neurology (AAN) reaffirmed the currency of the guideline in July 2016.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (Class I-IV) are provided at the end of the "Major Recommendations" field.

Question 1: Are there effective nonpharmacologic treatments for muscle cramps?

- Conclusion. Data are insufficient to draw any conclusion on the efficacy of calf stretching in reducing the frequency of muscle cramps.
- Recommendation. None (Level U).

Question 2: Is quinine effective in the treatment of muscle cramps?

- Conclusion. On the basis of data from 2 Class I studies, quinine derivatives are effective in reducing the frequency of muscle cramps, although the magnitude of benefit is small. Moreover, these agents are associated with serious though uncommon side effects.
- Recommendation. Although likely effective (Level A), the use of quinine derivatives for treatment of muscle cramps should be avoided for routine treatment of cramps. These agents should only be considered when cramps are very disabling, no other agents relieve symptoms, and there is careful monitoring of side effects. They should only be used after informing the patient of the potentially serious side effects.

Question 3: Are there any other pharmacologic treatments effective for the treatment of muscle cramps?

- Conclusion. On the basis of single Class II studies, naftidrofuryl, vitamin B complex, and diltiazem are possibly effective in the treatment of muscle cramps. Naftidrofuryl is currently not available in the United States. Data regarding the use of magnesium preparations (2 Class II studies) and gabapentin (1 study in amyotrophic lateral sclerosis [ALS]) show that these agents are probably not effective in the treatment of muscle cramps.
- Recommendation. Naftidrofuryl, diltiazem, and vitamin B complex may be considered for the treatment of muscle cramps (Level C).

Definitions:

Classification of Recommendations

Level A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Classification of Evidence for Studies of Therapeutic Intervention

Class I = A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required:

a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias
e. For non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
    1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
    2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment. (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
    3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
    4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II = A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III = All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV = Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

*Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Idiopathic muscle cramps

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Geriatrics

Internal Medicine

Neurology

Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To provide evidence-based recommendations for symptomatic treatment of idiopathic muscle cramps

Target Population

Patients with idiopathic muscle cramps

Interventions and Practices Considered

1. Quinine derivatives
2. Naftidrofuryl
3. Diltiazem
4. Vitamin B complex

Note: Calf stretching was considered but not recommended.

Major Outcomes Considered

- Incidence of painful muscle cramps
- Efficacy of therapy
- Adverse effects of therapy

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

2010 Guideline

The main search strategy was a comprehensive search of MEDLINE and EMBASE from 1950 to May 31, 2008, using the search term "muscle cramp" limited to keywords "therapy," "drug therapy," and "prevention and control," which yielded 558 results in 4 languages (including French, German, Spanish, and English). Additional articles were identified by cross referencing bibliographies from meta-analyses, review articles, and case reports identified in the initial search, which yielded 5 additional articles. "Muscle cramp" was defined as a sustained, generally painful, involuntary contraction of a muscle or muscle group. "Cramps" alone was not used as a search term due to excessive articles on gynecologic and gastrointestinal cramps.

The abstracts and titles from the 563 articles identified were reviewed, and a study was included if it was a prospective clinical trial with effect on muscle cramps as a primary or secondary outcome. Exclusion criteria were 1) review articles, 2) meta-analyses, 3) case reports or case series that did not involve a treatment, 4) phenomena not consistent with muscle cramps, such as muscle spasms, dystonia, or muscle pains, 5) pregnancy-induced cramps, 6) medical conditions such as hemodialysis and cirrhosis, and 7) cramps due to extreme physiologic stress such as excessive exercise, heat, or dehydration. Cramps secondary to medical conditions were excluded from this analysis because the mechanisms underlying the formation of cramps and often the treatment directed to correct them are distinct from the routine treatment of muscle cramps, and most treatment trials assessing idiopathic cramps also excluded these conditions. Muscle cramps due to myopathies were also excluded due to the distinct underlying mechanisms.

A total of 50 potential studies were identified for full review. Full review of the articles led to further exclusion of 26 articles that were review articles, letters, or repeat publications of the same clinical trials. The remaining 24 articles were chosen for inclusion in the final review, including one article dealing with nonpharmacologic therapy, 5 open-label pharmacologic trials, and 18 randomized pharmacologic trials.

2013 Reaffirmation

The Medline and Cochrane databases were searched from 2010 February 23 to 2013 July 13, using the following terms: "muscle cramp" limited to keywords "therapy," "drug therapy," and "prevention and control." Exclusion criteria were 1) review articles, 2) meta-analyses, 3) case reports or case series that did not involve a treatment, 4) phenomena not consistent with muscle cramps, such as muscle spasms, dystonia, or muscle pains, 5) pregnancy-induced cramps, 6) medical conditions such as hemodialysis and cirrhosis, and 7) cramps due to extreme physiologic stress such as excessive exercise, heat, or dehydration. A study was included if it was a prospective clinical trial with effect on muscle cramps as a primary or secondary outcome.

2016 Reaffirmation

The Medline database was searched from January 2013 to July 2016 using the following search terms: (muscle cramps) AND treatment. Inclusion criteria were RCTs, humans only, relevant to clinical questions; exclusion criteria used to screen search results were the same as described in the 2010 published guideline.

Number of Source Documents

24

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence for Studies of Therapeutic Intervention

Class I = A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required:

a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias
e. For non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
    1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
    2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment. (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
    3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
    4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II = A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III = All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV = Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

*Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

The final 24 articles (the source documents) involving symptomatic treatment of cramps were distributed to all 3 panel members for critical analysis and classification. Each member of the panel made an independent determination of class of evidence and a final meeting was called to discuss the articles and resolve differences. Data regarding cohort size, completion rate, inclusion and exclusion criteria, treatment and dosage, design of the study, length of study, primary and secondary outcomes, efficacy, and effect size were extracted from each article and tabulated (table e-1 on the Neurology® Web site at www.neurology.org). Each article was classified according to the American Academy of Neurology therapeutic classification of evidence scheme (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

2010 Guideline

Recommendations were based on the level of evidence (see the "Rating Scheme for the Strength of the Recommendations" field).

2013 Reaffirmation

An author conducted a literature search using the same criteria as presented in the original guideline. Because the guideline recommendations would not changes given the new literature available, the committee voted to reaffirm the guideline, stating that the conclusions and recommendations are still valid.

2016 Reaffirmation

A Guideline Development, Dissemination, and Implementation (GDDI) Subcommittee member who had expertise in neuromuscular disease conducted a targeted literature search for high quality studies using the same criteria as presented in the original guideline. The GDDI reviewer and the subcommittee reviewed the new evidence and determined that the following three criteria were met: 1. There is no new evidence that would alter conclusions or recommendations in the guideline since the last literature search, 2. Guideline methodology is sound and current methodology is not substantially different, and 3. No significant practice variation relevant to the guideline currently exists.

Rating Scheme for the Strength of the Recommendations

Classification of Recommendations

Level A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) reviewed and approved a draft of the article. The draft was next sent to members of the Practice Committee of the AAN for further review and then to Neurology® for peer review. Boards of the AAN reviewed and approved the final version of the article. At each step of the review process, external reviewers' suggestions were explicitly considered. When appropriate, the expert panel made changes to the document.

The guideline was approved by the Therapeutics and Technology Assessment Subcommittee on April 28, 2009, by the Practice Committee on July 1, 2009 and by the AAN Board of Directors November 9, 2009.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate choice of a treatment for patients with symptomatic idiopathic muscle cramps

Potential Harms

- The reported side effects in case reports and prospective trials using quinine sulfate or derivatives are listed in the table in the original guideline document. The most common serious side effects reported were hematologic abnormalities such as hemolytic uremic syndrome–thrombotic thrombocytopenia purpura, disseminated intravascular coagulation, and bleeding diathesis. These agents should only be used after informing the patient of the potentially serious side effects.
- Treatment with naftidrofuryl included mild gastrointestinal discomfort.

Contraindications

Contraindications

Quinine derivatives should be avoided for routine use in the management of muscle cramps because of the potential for toxicity.

Qualifying Statements

Qualifying Statements

This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the

circumstances involved.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Foreign Language Translations

Patient Resources

Quick Reference Guides/Physician Guides

Resources

Wall Poster

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Katzberg HD, Khan AH, So YT. Assessment: symptomatic treatment for muscle cramps (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2010 Feb 23;74(8):691-6. [36 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2010 Feb 23 (reaffirmed 2016 Jul 16)

Guideline Developer(s)

American Academy of Neurology - Medical Specialty Society

Source(s) of Funding

American Academy of Neurology (AAN)

Guideline Committee

Therapeutics and Technology Assessment Subcommittee

Composition of Group That Authored the Guideline

Guideline Authors: Hans D. Katzberg, MD; Ahmir H. Khan, MD; Yuen T. So, MD, PhD

Therapeutics and Technology Assessment Subcommittee Members (2007-2009): Janis M. Miyasaki, MD, MEd, FAAN (*Co-Chair*); Yuen T. So, MD, PhD (*Co-Chair*); Richard M. Camicioli, MD; Vinay Chaudhry, MD, FAAN; Richard M. Dubinsky, MD, MPH, FAAN; Cynthia L. Harden, MD; Cheryl Jaigobin, MD; Irene L. Katzan, MD; Barbara S. Koppel, MD, FAAN; James C. Stevens, MD, FAAN (Ex-Officio); William H. Theodore, MD, FAAN.

Financial Disclosures/Conflicts of Interest

Disclosure

Dr. Katzberg has received funding for travel from the Muscular Dystrophy Association. Dr. Khan reports no disclosures. Dr. So receives royalties from the publication of Occupational & Environmental Medicine (Appleton & Lange, 2007) and articles published in UpToDate (2007); receives research support from Pfizer Inc, NeurogesX, Inc., and the NIH (NIEHS R01 [Co-I], NIEHS R01 [Co-I], and NINDS R01 [Site PI]); estimates 10% of his clinical effort is spent on EMG; and holds equity in Satoris, Inc.

Conflict of Interest

The American Academy of Neurology (AAN) is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, Neurology® peer reviewers and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com .

Guideline Endorser(s)

American Association of Neuromuscular and Electrodiagnostic Medicine - Medical Specialty Society

Guideline Status

This is the current release of the guideline.

The American Academy of Neurology (AAN) reaffirmed the currency of the guideline in July 2016.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

A list of American Academy of Neurology (AAN) guidelines, along with a link this guideline, is available at the AAN Web site .

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 201 Chicago Avenue South, Minneapolis, MN 55415.

Availability of Companion Documents

The following are available:

- Symptomatic treatment for muscle cramps. AAN summary of evidence-based guideline for clinicians. St. Paul (MN): American Academy of Neurology. 2010. 1 p. Available from the American Academy of Neurology (AAN) Web site .
- Assessment: symptomatic treatment for muscle cramps. Poster. St. Paul (MN): American Academy of Neurology. 2010. 1 p. Available from the AAN Web site .
- AAN guideline development process [online]: Assessment: symptomatic treatment for muscle cramps (an evidence-based review); St. Paul (MN): American Academy of Neurology. Available from the AAN Web site .

In addition, a Chinese translation of the original guideline document is available from the *Neurology* journal Web site .

Patient Resources

The following is available:

- Drug treatments for symptoms of muscle cramps. AAN summary of evidence-based guideline for patients and their families. 2010. 2 p. St. Paul (MN): American Academy of Neurology. Available from the American Academy of Neurology (AAN) Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This summary was completed by ECRI Institute on August 30, 2010. The currency of the guideline was reaffirmed by the developer in July 2013 and the summary was updated by ECRI Institute on December 22, 2015. The currency of the guideline was reaffirmed by the developer in July 2016 and the summary was updated by ECRI Institute on January 18, 2017.

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